REMARKS

Claims 1, 3-6, and 8-45 are pending in the application. New claims 28-45 have been added. Claims 1, 3-6, and 8-27 are under active consideration.

Claim 13 has been amended to recite "poly(D,L-lactide-co-glycolide) (PLG)." Support for this amendment can be found in the specification, for example, at page 23, line 23 through page 24, line 1, which describes PLG as an abbreviation for poly(D,L-lactide-co-glycolide copolymer. Applicant is amending the claim solely to obtain expeditious allowance of the instant application and not for reasons related to patentability.

Support for new claims 28-45 can be found in the original claims and throughout the specification. Entry of the new claims is therefore respectfully requested.

Amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 102.

Status of Office Action

Although, the Office Action Summary page of the Office Action mailed June 15, 2005 indicates that the Office Action is final, Examiner Myron Hill indicated in a telephone conversation on August 12, 2005 that this Office Action is non-final. Applicants are acting accordingly on Examiner's assertion that this Office Action is not final.

Objection to the Claims

Claim 13 is objected to on the grounds that the full terminology for the abbreviation "PLG" is required to appear the first time it is recited in the claims. To expedite prosecution, claim 13 has been amended to make explicit that PLG is an abbreviation for a poly(D,L-lactide-co-glycolide) copolymer.

Rejection under 35 U.S.C. § 103

Claims 1, 4-6, 8-10, 14, 15, 17, and 26 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Houghton et al. (EP0318216) and Fields Virology. In particular, the Office Action alleges that "it would have been *prima facie* obvious to use the E2 and/or E1E2 regions as taught by Fields in the method of Houghton et al. to elicit a humoral immune response with the expectation of success because Houghton et al. teach that those regions will give rise to antibodies" (Office Action, page 4).

In addition, claims 3 and 18-25 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Houghton et al. (EP0318216), and Fields Virology, and further in view of Ishii et al., *Hepatology* (1998) 28:1117-1120. In particular, the Office Action alleges that "Ishii et al. teach that antibodies to envelope (E2) give rise to NOB antibodies and that the titer can be at least 3000" (Office Action, page 5).

In addition, claims 11-13, 16, and 27 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Houghton et al. (EP0318216), and Fields Virology, and further in view of Fomsgaard et al. APMIS (1998) 106:636-646 (Applicants assume this is the reference intended) or Singh et al. In particular, the Office Action alleges:

> One of ordinary skill in the art at the time of invention would have been motivated to use art known modifications to the method for administering DNA. The use of agents to prepare the site for DNA inoculations is known in the art, such as cardiotoxin (see Nielson, AMPIS 1998, previously cited) as well as various methods to prepare DNA for inoculation, including different forms of microparticles, including PLG (Singh et al., abstract). In the art of vaccination and immunization studies, boosting with protein after DNA vaccination is also known (Barnett et al., abstract).

Applicants respectfully traverse the rejections under 35 U.S.C. § 103 on the following grounds.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In

addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

Applicants submit that the cited references do not disclose or suggest all the limitations of the present invention. Thus, a *prima facie* case of obviousness has not been presented by the Office, and the cited combination is based on impermissible hindsight reconstruction.

Claim 1 is drawn to a method of eliciting a humoral immune response against a hepatitis C virus (HCV) E2 or E1E2 antigen comprising administering to a subject a composition comprising an isolated polynucleotide encoding an HCV E1E2 antigen or a full-length E2 antigen, wherein the E2 or E1E2 antigen encoded by the polynucleotide is produced intracellularly and not secreted when expressed in cells of the subject. Some of the dependent claims further require that the humoral immune response generate neutralization of binding (NOB) antibodies.

Houghton fails to describe or suggest a method of eliciting a humoral immune response by administering to a subject a composition comprising an isolated polynucleotide encoding E2 or E1E2 antigens, wherein the E2 or E1E2 antigen encoded by the polynucleotide is produced intracellularly and not secreted when expressed in cells of the subject. Moreover, Houghton is silent on the importance of delivering polynucleotides that encode E2 and E1E2 antigens that are specifically produced intracellularly and not secreted, wherein a humoral immune response generates NOB antibodies in the subject. In contrast, the instant application provides evidence that higher levels of NOB antibodies can be produced in a subject by administering polynucleotides encoding E2 and E1E2 antigens that are expressed intracellularly compared to polynucleotides encoding antigens that are secreted. See specification, for example, at Examples 1-4. The secondary references also fail to teach such methods.

Fields Virology fails to teach or suggest any method of administration of polynucleotides encoding E2 or E1E2 antigens for eliciting a humoral immune response against hepatitis C virus. Furthermore, Fields Virology fails to teach the use of polynucleotides expressing the precisely claimed E2 or E1E2 antigens having sequences

corresponding to amino acids 192-746, 192-809, or 384-746 numbered relative to the HCV-1 polyprotein. Nor does Fields Virology teach or suggest the importance of administering polynucleotides encoding antigens that are not secreted.

Ishii et al. fail to teach or suggest any method of administering polynucleotides encoding E2 or E1E2 antigens that are expressed intracellularly, as required by the claims. Rather, Ishii et al. discovered that a rare group of patients, who recovered from HCV infection, had NOB antibodies, unlike most patients who succumb to chronic infection. Notably, Ishii et al. found that most patients, who fail to clear the virus and resolve HCV infection, developed low or no NOB antibodies (see abstract). Ishii et al. do not, however, disclose or suggest any method of eliciting NOB antibodies in patients not producing such antibodies naturally.

The references of Fomsgaard et al. and Singh et al. are not directly applicable to methods of treating HCV infection. Fomsgaard et al. fail to describe or suggest methods of DNA vaccination against HCV infection. Singh et al. fail to describe or suggest the use of PLG microparticles for administration of E2 or E1E2 antigens.

Applicants emphasize the importance of administering isolated polynucleotides expressing E2 or E1E2 antigens intracellularly for eliciting antibodies that inhibit HCV receptor binding to cells, *i.e.*, NOB antibodies. See specification, for example, at page 17, lines 15-29, and Table 3 at page 38. In contrast, some of the prior art can be described as teaching away from the claimed invention in that others have found that secreted forms of E2 show greater antigenicity (see specification, for example, at page 17, lines 1-14).

Thus, the references do not disclose or suggest all the limitations of the present invention, and the Examiner has not met the burden of establishing a *prima facie* case of obviousness. In the absence of some teaching or suggestion in the cited references concerning methods of eliciting a humoral immune response against hepatitis C virus (HCV) by administering polynucleotides encoding E2 or E1E2 antigens that are not secreted, as described in the present application, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. As stated by the Court of Appeals for the Federal Circuit *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir.

1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103. For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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